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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,296	03/21/2001	Laura L. Kiessling	1-00	4642

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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/815,296	KIESSLING ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya, Ph.D.	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *43,61,63,65,69,70,89 and 156* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17, 21-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 90-92, 140-148, 150, and 157-163* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/27/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

Continuation of Disposition of Claims: Claims pending in the application are 17,21-23,28-30,41-43,59-61,63-65,68-74,89-92,140-148,150 and 156-163.

DETAILED ACTION

1. Application No. 09815296 (20030125262 A1): Claims 17, 21-23, 28-30, 41-43, 59-61, 63-65, 68-74, 89-92, 140-148, 150, and 156-163 are pending. Claims 43, 61, 63, 65, 69, 70, 89, 156 are withdrawn from consideration. Claims 17, 21-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 90-92, 140-148, 150, and 157-163 are examined.

Nucleotide/Amino Acid Sequences

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Particularly, the specification contains sequences, including SEQ ID No.s, (see, e.g., p. 40) and Formula 21 of Scheme 2. However, no paper copy of any sequence listing and no corresponding computer readable form appears in the record. Correction is required as part of a complete response to the instant Office action.

Withdrawn Claim Objections/Rejections

3. The following claim objections/rejections are withdrawn:

4. Claim 161 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Priority

5. This application, 09/815,296, filed 3/21/2001, claims benefit of 60/191,014, filed 3/21/2000.

Information Disclosure Statement

6. The IDS, entered 9/27/06, has been considered.

Specification

7. The disclosure is objected to because of the following informalities: Compound 21 in Scheme 2 appears to fall within the amino acid sequence rules, and so must be provided a sequence identifier number ("SEQ ID No.").

Appropriate correction is required.

8. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because the abstract contains too many words. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112, First Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 17, 21-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 90-92, 140-148, 150, and 157-163 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

This rejection is maintained for the reasons of record, as set forth in the previous Office action. This rejection is necessitated by applicant's amendments to the claims.

The specification as filed does not appear to provide support for methods comprising signal recognition elements that are an N-formyl peptide or an N-acyl

peptide, which induces the release of an intracellular signal and wherein the intracellular signal induces cellular chemotaxis. Applicant must point, with particularity, where support for this limitation may be found in the specification as filed.

Response to Arguments

Applicant argues that specification teaches the limitation of cellular chemotaxis. Applicant argues that cellular chemotaxis induction by intracellular signals is found in the specification. Applicant's arguments assert that "[s]uch direct signaling is by an intracellular signal. Ligand-mediated binding to a cell-surface receptor is known in the art to be regulated by release of an intracellular signal, such as by Ca^{2+} for example", (Reply at p. 15). Applicant refers to lateral clustering and chemotactic activity. Applicant states that neutrophils can bind N-formyl peptide to undergo chemotaxis vial intracellular signaling and states that "[t]he specification implicitly recognizes that neutrophils responds to both intracellular and intercellular signals when undergoing chemotaxis", (Reply at p. 16).

Applicant's arguments, entered 1/17/2007, have been fully considered but they are not persuasive. Applicant argues that cellular chemotaxis by intracellular signal are known in the art to be regulated by an "intracellular signal, such as by Ca^{2+} for example". These arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence

that is required to rebut a *prima facie* case of obviousness."). MPEP 2145.The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145.

Furthermore, the specification does not disclose that cellular migration or chemotaxis is a intracellular *response*, (see, Specification at para [0048]), but the specification as filed does not appear to disclose that cellular migration or chemotaxis is *induced* by an intracellular *signal*. The specification discloses intracellular signals as associated with transduction systems, and states:

> [0058] Multivalent ligands of this invention can be used to modulate signal transduction in prokaryotic and eukaryotic organisms. The ligands function in a variety of signal transduction processes. Prokaryotes have a highly conserved **intracellular signal transduction** system, the two component system. The major components of this system are varying numbers of alternating histidine-aspartic acid kinase-mediated phosphorylation events, such as virulence, antibiotic resistance, response to environmental stress and sensing. The components of the two component system are highly conserved in prokaryotes. In contrast, eukaryotes appear to have very few two component systems for signal transduction. This orthogonality makes the two component signaling pathway a prime target for exploitation in therapeutic design for the control of bacterial infection.

> **Major signal transduction systems in eukaryotes are mediated by G-protein-linked receptors and enzyme-linked receptors (including receptor guanylyl cyclases, receptor tyrosine kinases, tyrosine-kinase-associated receptors, receptor tyrosine phosophatases, and receptor serine/threonine kinases)**. The ability to modulate or regulate signal transduction in these pathways allows control over a wide variety of biological processes in eukaryotic cells and eukaryotic organisms (including mammals and specifically humans) and provides significant opportunity for the design of therapeutics.

Specification, at p. 17, line 19-p. 18, line 2, (para [0058]).

The Specification, at p. 18, line 4-5, teach that a multivalent ligand can be involved in signaling; and at p. 18, lines 10-14, teach the *disruption* of cell migration by multivalent ligands functioning through direct signaling. However, the specification does not appear to disclose the *induction* of cellular chemotaxis by intracellular signals.

The Specification at p. 38, lines 15-30 [para 0122] , teaches neutrophil migration response to N-formyl peptides, and teaches the release of *inter*cellular signals, but does not appear to teach *intra*cellular signals as associated with N-formyl peptides. The specification does not appear to disclose that all chemotaxis or cellular migration involves intracellular signals. Therefore, the specification as filed does appear to provide support for the induction of cellular chemotaxis by intracellular signal by the introduction of N-formyl peptide.

Furthermore, the claimed methods encompass the use of multivalent ligands that do not comprise an SRE, wherein the methods induce intracellular signals that induce cellular chemotaxis and wherein N-formyl peptides are SRE. The specification as filed, however, does not appear to provide support for the induction of intracellular signals or cellular chemotaxis by ligands that are not SRE or N-formyl peptides.

11. Claims 17, 21-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 90-92, 140-148, 150, and 157-163 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for lack of written description.

This rejection maintains the reasons of record as set forth in the previous Office action and is extended to claims not previously rejected for lacking written description. The rejection is copied for the convenience of the reader.

The claims are broadly drawn to methods for inducing a biological response in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements (see claim 1). The specification (at p. 27, lines 18-20) contemplates, methods wherein the multivalent ligands of the instant invention are useful "for controlling or modulating the effect of chemical signals in a biological system." The specification, at p. 27, lines 19-23, states that the instant disclosure exemplifies application of "multivalent ligands to bacterial and eukaryotic chemotaxis, to migration of leukocytes (particularly neutrophils), to immune responses of B-cells and T-cells, to cell aggregation, and to signaling of apoptosis." Actual working embodiments (specification at p. 45, line 21-p. 50, line 27 and pp. 60-64, Scheme 1-Scheme 5) involve saccharide ligands for chemotaxis in *E. coli* and concanavalin A-mediated agglutination in Jurkat T cells and erythrocytes and PC12 cell cytotoxicity experiments.

The specification does not describe a sufficient number of species of responses induced by multivalent ligands to be representative of the genus of intracellular signals and/or the vast genus of biological responses.

Vas-Cath Inc. v. Mahurkar, 19 USPQ 2d 1111, 1117, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

To provide adequate written description and to provide evidence of possession of a claimed genus, the specification must provide a representative number of species. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus and describe sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and / or chemical properties, functional characteristics, structure / function correlation, methods of making the claimed product, and combinations thereof.

The broad genus of methods inducing a biological responses using multivalent ligands admits to substantial variation that would include virtually any biological response. The specification exemplifies five general categories (chemotaxis, leukocyte migration, immune response, cell aggregation and apoptosis) and provides working examples of as few as two multivalent ligands (a saccharide and concanavalin A). The specification describes an intracellular signal transduction system that is a two component found in prokaryotes. The examiner respectfully submits that the examples are not so

comprehensive as to be representative of the full scope of the claimed genus. The specification does not disclose that N-formyl peptides act as mitogens, or that they effect the release of calcium as an intracellular signal, as in claims 152 and 153. Furthermore, the rejected claims recite little molecular structure or identity for the receptors, signal recognition elements, or molecular scaffold. Accordingly, the specification does not provide adequate written description of the claimed genus of methods inducing biological responses, comprising receptors, ligands, and molecular scaffolds.

The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of all multivalent ligands that bind to any receptor to induce any biological response, and given the few actual examples provided and the unpredictability of the ligand-receptor and medicinal drug art, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making and using multivalent ligands. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The multivalent ligands themselves are required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, at 1483 (finding claims directed to *mammalian* FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the *bovine* sequence).

Therefore, only the methods comprising specific multivalent ligands that bind to cellular receptors to induce chemotaxis or agglutination, as taught by the instant specification, but not the full breadth of the claim, meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Response to Arguments, 3/24/2006

Applicant argues the formulas, structures, examples and description regarding synthesis of the ROMP-based multivalent ligands containing n-formyl and N-acyl peptides provide a written description that is sufficient in view of what is known in the art about such polymers and derivatized peptides that the skilled artisan would consider that the applicant was in possession of the invention as now claimed at the time the application was filed, (Reply at p. 23, para 1). Applicant points to p. 40 of the specification for the teaching that N-formyl peptides function as chemoattractants and that certain cells release "*intercellular* signals that affect responses in other cells and that this is particularly observed in immune systems cells" [emphasis added], (Reply at p. 20, para 2). Applicant points statements found in the specification at pp. 9, 15-16, teaching N-formyl peptides or N-acyl peptides as inducing the release of signals from cells, (see Reply at p. 21). Applicant argues that if the statements are considered reasonable to support enablement, they should be sufficiently reasonable to also support written description.

Applicant's arguments entered 12/13/2005 have been fully considered but they are not persuasive. Applicant's arguments regarding *intercellular* signals do not address claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140, 142, 143, 148, 150-155, 157, and 162-164, drawn to *intracellular* signals. The examples and teachings that applicant points to for intercellular signal systems between cells, do not provide a representative number of species to adequately describe the vast genus of any "biological response", as in claims 141, 144-147, and 158-161.

In regard to applicant's argument that if the statements are considered reasonable to support enablement, they should be sufficiently reasonable to also support written description, the examiner respectfully resubmits that "Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115)", (as stated in the previous Office action).

Response to Arguments

Applicant arguments appear to state that the instant rejection is overcome by the new amendments to claims clarifying that the invention is for inducing intracellular

signals which induce cellular chemotaxis. Furthermore, applicant's argument states that further amended claim 28 provides "detailed chemical structure of the multivalent ligand".

Applicant's arguments, entered 1/17/2007, have been fully considered but they are not persuasive. The claims as amended continue to lack written description. The specification as filed, does not provide a representative number of N-formyl peptides adequate to describe the genus "signal recognition elements" (SRE) in a multivalent ligand of the claimed invention, wherein the multivalent ligand induces an intracellular signal, which in turn, induces cellular chemotaxis, such that one of skill in the art would envision that applicant had possession of the claimed methods.

Claim Rejections - 35 USC § 112, Second Paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 17, 21-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 90-92, 140, 142, 143, 148, 150, and 156, 157, 162 and 163 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by applicant's amendments to the claims.

Claim 28, and its dependent claims, are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative

relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the relationship of signal recognitions elements, N-formal peptides or N-acyl peptides, when the newly claimed multivalent ligand, has values of R^1 and R^2, is does not comprise an SRE. The multivalent ligand of claim 28 states limitations that do not necessarily include SRE, so that it is unclear where an N-formyl peptide is to be found if, for example, when each of R^1 and R^2 are independently hydrogen (H).

Maintained Claim Rejections - 35 USC § 103

14. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

15. Claims 17, 21-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 90-92, 140-144, 148, 150, 157, 159, and 161-163 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Whitesides** et al., WO 98/46270 (reference 4, IDS filed 10/10/2002), **Arimoto** et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11), and further in view of **Painter** et al., Journal of Cell Biology, 1987, vol. 105, pp. 2959-2971, (of record).

This rejection maintains the reasons of record as set forth in the previous Office action. This rejection is extended to claims newly added by amendment. The rejection is copied below for the convenience of the reader.

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal recognition elements are bonded to molecular scaffold, and wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide, as in claims 66, 84 and 150.

Whitesides et al., teach methods for inducing a biological response using multivalent ligands, including ligands where the signal recognition element is a peptide, as presented above.

Arimoto et al., teach methods for inducing a biological response by multivalent ligands having the structure as formulated as in claim 144, as presented above.

Neither of Whitesides et al. or Arimoto et al., as above, teach methods for inducing a biological response by multivalent ligands, wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide.

Painter et al., teach a derivatized peptide that is an N-formylated peptide that is a ligand that binds to a glycoprotein receptor and acts as a recognition element to stimulate chemotaxis of human neutrophils.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to combine methods of comprising inducing biological response by multivalent ligands that bind to receptors, wherein such methods comprise ligands with derivatized or N-formylated peptides.

One of ordinary skill in the art would have been motivated to use methods comprising derivatized or N-formylated peptides in multivalent ligands in order to stimulate chemotaxis of human neutrophils, as taught by Painter et al. One of ordinary skill in the art would have had a reasonable expectation of success, because N-formylation of peptides was long known in the art, as was the formylated peptide induction of neutrophil chemotaxis.

Response to Arguments, 3/24/2006

Applicant argues that the reference of Whitesides et al. does not specifically disclose multivalent ligands containing N-formyl peptides and no specific disclosure of the use of such ligands for inducing the release of a signal from a cell. Applicant argues that there is no specific enabling teaching of the use of any polymer presenting N-formyl peptides in the reference of Whitesides et al.

Applicant argues that the reference of Arimoto et al. does not teach or suggest that any strengthening of the binding interaction by use of a polyvalent species would have any beneficial effect on the induction of an intracellular signal by N-formyl peptides.

Applicant argues that the reference of Painter et al. does not teach or suggest that any polymer containing an N-formyl peptide would retain the function of the N-formyl peptide to stimulate chemotaxis of human neutrophils and further that there is no teaching that any benefit could be obtained by presenting an N-formyl peptide to the neutrophil in a polyvalent manner.

Applicant's arguments entered 12/13/2005, have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Whitesides et al. teach the making and use of multivalent ligands produced by ROMP technology, and wherein the ligand can be a peptide. The reference of Arimoto teaches the use of multivalent ligands produced by ROMP technology, including the particular structures of claims 144 and 162. The reference of Painter et al. teaches and suggests that N-formyl oligopeptides as members of a class of peptides which initiate a variety of rapid biochemical and cellular responses that include the positive chemotaxis of human neutrophils. Absent objective evidence to the contrary, there would have been a reasonable expectation of success in making multivalent ligands comprising N-formyl peptides, because Whitesides et al. teach that the ligand can be a peptide, and Painter et al. teaches that N-formyl peptides are a class of peptides. Applicant offers no objective evidence, notwithstanding arguments of counsel, that N-formyl peptides would not be considered suitable by one of ordinary skill in the art, for use in multivalent ligand

compounds for inducing a variety of biochemical and cellular responses, including chemotaxis of human neutrophils.

Response to Arguments

Applicant arguments state that the results of the presently claimed invention are "unexpected". Applicants emphasize that Painter teaches isolated N-formylated peptides binding neutrophil receptor, but does not teach N-formylated peptide bound to a molecular scaffold, is able to induce cellular chemotaxis. Applicant argues that Whitesides does not provide evidence that cellular chemotaxis can be induced using multivalent ligands comprising peptides. Applicant argues that Arimoto does not provide any indication that an N-formylated peptide bound to a molecular scaffold can induce cellular chemotaxis.

Applicant's arguments, entered 1/17/2007, have been fully considered but they are not persuasive. Applicant's representative provides no objective evidence of unexpected results. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Whitesides, e.g., at pp. 1-2, discloses the desirability of polyvalency in eliciting ligand-receptor binding events. Whitesides, at p. 2, discusses the generation of multivalent carbohydrates involved in viral adhesion to the surfaces of cells. Whitesides describes polyvalent presenters for cell adhesion assays, agglutination assays, platelet aggregation assays, and lymphocyte stimulations assays.

Painter teaches N-formylated peptides activates protein kinases in inducing chemotaxis of human neutrophils, thereby teaching intracellular signaling, (see, instant Specification, at p. 17, line 19-p. 18, line 2, (para [0058]).

16. Claims 17, 21, 22, 28-30, 41, 42, 59, 60, 64, 68, 74, 90-92, 142-144, 150, 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Gordon et al.**, Chemistry & Biology, vol. 7:9-16, 2000 (of record), in view of **Schiffman et al.**, US 4,427,660, (of record).

This rejection maintains the reasons of record as set forth in the previous Office action. This rejection is extended to claims newly added by amendment. The rejection is copied below for the convenience of the reader.

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements bonded to molecular scaffold and wherein the signal recognition elements are recognized by at least one of the receptors, wherein one or more of the signal recognition elements is an N-formyl peptide, and variations thereof.

Gordon et al., throughout the publication and at the abstract, p. 9, para 4-p. 10, para 2, teach using ring-opening metathesis polymerization (ROMP) to generate to form multivalent arrays that include

multivalent ligands for binding to cell surface receptors; teach at Figures 3-5, polymers of the general formula of claims 82, 91 (e.g., m=0 and n=2 or more) and 144; at p. 13, para 2 and 3, teach multivalent ligands coupled to a fluorescent reporter group that is fluoresce in, where the signal recognition element binds to L-selectin, which acts to recruit white cells to sites of tissue damage, and so acts as a guide to cells, i.e., chemoattractant, as demonstrated on human T-cells (Jurkat cells).

Gordon at p. 9, para 2 and 3 teaches that attachment of assemblage of biologically active multivalent ligands, and that multivalent recognition events have importance in biology. Gordon at p. 10 teaches ligands that target selectins and that selectins are cell-surface proteins that facilitate the recruitment of leukocytes to sites of inflammation, that selectins have been inhibited with multivalent ligands, and that multivalent ligands have greater potency than monovalent counterparts. Gordon at p. 10-p. 11, bridging paragraph, and p. 13, para 4, cites references showing that L-selectin recruitment of white blood cells to cites of inflammation was known in the art and teaches a neoglycopolymer bearing a 3,6-disulfogalactose epitope (as in claim 86), such as compound **11a** and its reporter derivative, compound **16**, (see also Fig. 5) as multivalent ligands of L-selectin. Also, the instant Specification states: "Most non-self proteins and many carbohydrates are antigens, so epitopes, without limitation, proteins fragments (e.g., peptides) and carbohydrate fragments (e.g., saccharides and oligosaccharides)." Specification at p. 15, line 26-29. Therefore, the saccharide ligands taught by Gordon are epitopes. Gordon at pp. 13-14, bridging paragraph, states the multivalent ligands taught have biological activities that range from their function as effective inhibitors of the selectins to molecules that promote L-selectin downregulation from the cell surface. Gordon at p. 13, para 3-4, teaches neoglycopolymer reporter ligand **16** as binding Jurkat cells, and teaches that these neoglycopolymers inhibit L-selectin-mediated cell rolling. Gordon at p. 10, para 2 and p. 11, para 1, teaches that selectins recruit leukocytes to sites of inflammation, reading on chemoattraction (as in claim 85) and that selectins are mucin-like proteins that present multiple copies of anionic saccharide epitopes, and that neoglycopolymers, such as compound **11**, mimic mucins, and inhibit selectins by adopting structures similar to selectins, so that, absent evidence to the contrary, the multivalent ligands comprising compounds **11** and **16**, further mimic the chemoattractant properties of selectins.

The reference of Gordon et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide.

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Gordon et al. and Arimoto et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

Response to Arguments

Applicant argues that there is no expectation of success that binding N-formyl peptides to a multivalent ligand would result in functional induction of cellular chemotaxis, because Schiffman teaches attaching a chemotactic agent to an antibiotic. Applicant argues that the unbound multivalent ligands (scaffold?) of the claimed invention is not a chemotactic agent, but applicant argues that Schiffman teaches that antibiotics can be, themselves, chemotactic agents.

Applicant argues that there is no motivation to combine Schiffman with the multivalent ligands of Gordon because the presently claimed invention is to induce a single biological function that is cellular chemotaxis, while Schiffman teaches bifunctional pharmaceuticals.

Applicant's arguments, entered 1/17/2007, have been fully considered but they are not persuasive. Applicant's arguments provide no clear reason why one of ordinary skill in the art would not have a reasonable expectation of success in combining the teachings of Gordon and Schiffman to arrive at the claimed method. The reference of Gordon et al., describe the use of multivalent ligands. Schiffman teaches the covalent conjugation of N-formyl peptides. Applicant's argument seems to be that antibiotics cannot be considered scaffolds, but Gordon et al., describe ROMP scaffolds.

Applicant's representative provides no clear objective evidence that a reasonable expectation of success is lacking. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA

1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Gordon et al., e.g., at p. 10, discloses the greater potency of multivalent ligands, as to so provide motivation for combination with the methods of Schiffman for the use of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4).

17. Claims 17, 21-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 90-92, 140-143, and 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Whitesides** et al., WO 98/46270 (reference 4, IDS filed 10/10/2002), in view of **Schiffman et al.**, US 4,427,660, (of record).

This rejection maintains the reasons of record as set forth in the previous Office action. This rejection is extended to claims newly added by amendment. The rejection is copied below for the convenience of the reader.

Whitesides, throughout the publication and at p. 3, lines 11-24, p. 7, lines 24-31, p. 14, lines 1-9, p. 15, lines 20-31, teaches multivalent ligands on a polymeric backbone of the form $Y-(A)_n$, where Y is a framework, A is a functional group, and n is an integer greater than 10, 50 or more, or about 100 or more

and wherein the functional group that is a signal recognition is covalently bonded to the framework that is a molecular scaffold, such as a liposome; teaches at p. 32, lines 7-13, polyvalent presenters that include Sialyl Le^x that bind leukocyte receptor sites including integrins and selectins and are elements involved in signal recognition, inducing intracellular and intercellular responses; teaches at p. 60, line 26-p.61, line 20 modulation of cell-cell interactions by polyvalent presenters, (which include multivalent ligands), whereby numerous cell-cell interactions can be promoted or inhibited, such as neutrophil attachment to endothelial cells during inflammation; teaches at Table 2, p. 62, line 4-p. 63, line 7, cell-cell interactions that comprise neutrophil, endothelial cells, T–cells, and the release of platelet granules; at p. 87, lines 3-18, teaches cytokine production by replacing a stimulator cell in a cell-cell interaction that normally leads to cytokine secretion, e.g., using L-selectin ligands to simulate monocytes and macrophages to produce tumor necrosis factor; teaches at p. 96, line 1-p. 99 line 16, *in vitro* assays; at p. 97, line 31- p. 99, line 16, teaches cross-linking multivalent receptors on the cell by agglutinins to prevent the biological response of viral binding to the cell surface.

Whitesides, for example, at p. 118-120, Example 5, p. 141, Figure 11, teaches methods for facilitating the treatment of influenza by inhibiting influenza-mediated hemagglutination comprising multivalent ligands of the formulas of claims 82 and 91 (where m=0 and n=2 or more), where SRE is NeuAc connected by a linker to a backbone repeating unit that is acyclic, R4-R6 are organic groups, and Z is H or an organic group.

Whitesides, at p. 93, line 18-p. 94, 12, teaches an intracellular signal transduction mechanism triggered by activation of certain G-protein coupled receptors that that mediates intracellular signal transduction (as in claims 18 and 19) and results in a reaction of the acrosomal exocytosis of sperm.

Furthermore, Whitesides at p. 4, lines 7-17, teaches, for example, methods for treating a disease or condition using polyvalent ligands, which read on effecting a biological response; or for treating a number of disease, Whitesides at p. 94, line 22-p. 95, line 9.

Whitesides, for example at p. 61, states that polyvalent presenters (reading on multivalent ligands) can be used to modulate cell-cell interactions and that numerous biological processes require cell-cell interaction that can be promoted or inhibited, and at Table 2, p. 62, list cells whose biological response may be so affected, said cells including neutrophils, endothelial, and cells, as in claims 20-23 and 30. Whitesides, for example at p. 94, lines 7-12, teaches an intracellular signal transduction mechanism triggered by activation of certain G-protein coupled receptors that results in a reaction of the acrosome of sperm, and at p. 94, lines 1-21, teaches using multivalent GlcNac ligands to induce acrosomal exocytosis of mouse sperm, that involves an intracellular signal, as in claims 28, 29, 154 and 155. Whitesides, for example at p. 87, lines 3-18, teaches the modulated release of cytokines by polyvalent ligands, as in claim 155. Whitesides, for example at p. 94, lines 7-8, teaches reorganization of cell surface receptors involved in fertilization, which reads on modulating a biological response, or at p. 97, line 31-p.99, line 15, teaches crossing linking multivalent receptors to prevent viral binding to cell surfaces, as in claims 41 and 42. Whitesides at p. 36, lines 9-22, teaches polyvalent ligands on solid supports, such as beads, that are useful in screening for a adhesion, or adhesion resulting in, for example, infection, cell death, cell proliferation, morphological change, etc., as in claim 140. Therefore, Whitesides et al., throughout the patent teach the claimed invention, as set forth above and in the previous Office action.

The reference of Whitesides et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide.

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Whitesides et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

Response to Arguments

Applicant argues that for the reasons previously presented against the reference of Whitesides, the claimed invention is unpatentable.

Applicant's arguments, entered 1/17/2007, have been fully considered but they are not persuasive. Applicant's representative provides no objective evidence of unexpected results. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Whitesides, e.g., at pp. 1-2, discloses the desirability of polyvalency in eliciting ligand-receptor binding events. Whitesides, at p. 2, discusses the generation of multivalent carbohydrates involved in viral adhesion to the surfaces of cells. Whitesides

describes polyvalent presenters for cell adhesion assays, agglutination assays, platelet aggregation assays, and lymphocyte stimulations assays.

Painter teaches N-formylated peptides activates protein kinases in inducing chemotaxis of human neutrophils, thereby teaching intracellular signaling, (see, instant Specification, at p. 17, line 19-p. 18, line 2, (para [0058]).

18. Claims 17, 21-23, 28, and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kiessling** et al., US 6,291,616, (reference 1, IDS filed 10/10/2002), in view of **Schiffman et al.**, US 4,427,660, (of record).

This rejection maintains the reasons of record as set forth in the previous Office action. This rejection is extended to claims newly added by amendment. The rejection is copied below for the convenience of the reader.

Kiessling et al., US 6,291,616, at col. 1, lines 10-48, teach using ring-opening metathesis polymerization (ROMP) to generate to form multivalent arrays that include multivalent ligands for binding to cell surface receptors, e.g. through epidermal growth factor, resulting in dimerization of the transmembrane receptor; teaches at col. 10, line 32-col. 11, line 46, polymers of the general formula of claims 82 and 91, col. 13, line 44-col. 14, line 32, teach multivalent ligands coupled to a fluorescent reporter group that is fluoresce in, where the signal recognition element binds to L-selectin, which acts to recruit white cells to sites of tissue damage, and so acts as a guide to cells, i.e., chemoattractant, as demonstrated on human T-cells (Jurkat cells).

Kiessling at col. teaches coupling an amine-containing saccharide moiety to yield a 3,6-disulfogalactose derivative to form neoglycopolymers. Kiessling at col. 13, lines 51-60, teaches that L-selectin facilitates the recruitment of white blood to sites of tissue damage and that these neoglycopolymers inhibit selectin function by binding to L-selectin on the cell surface. Kiessling at col. 14, lines 5-19, teaches that these neoglycopolymers bind to Jurkat cells, and at col. 14, lines 20-27, state: "Moreover, further microscopy studies suggest that the significant biological activities of these glycoprotein mimics are mediated through multivalent contacts." Thus Kiessling teaches methods comprising glycopolymer multivalent ligands that induce a biological response, as in the claimed invention. The term "biological response" is very broad and the specification and the claims do not provide a specific, limiting definition for the term

The reference of Kiessling et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl

peptides, particularly as medicinals and drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide..

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Kiessling et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

Response to Arguments

Applicant argues there is no teaching or suggestions that cellular chemotaxis can be induced by presenting a multivalent ligand having a signal recognition element that is N-formyl peptide.

Applicant's arguments, entered 1/17/2007, have been fully considered but they are not persuasive. Kiessling teaches multivalent ligands for increased binding, increased avidity, specificity, and unique inhibitory potencies; and so provides motivation for combination with the methods of Schiffman for the use of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4).

19. Claims 17, 21-23, 28, 59, 60, 64, 68, 74, 90-92, 144, 148, 150, 157, 159, and 161-163 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Arimoto** et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11), in view of **Schiffman et al.**, US 4,427,660, (of record).

This rejection maintains the reasons of record as set forth in the previous Office action. This rejection is extended to claims newly added by amendment. The rejection is copied below for the convenience of the reader.

Arimoto et al., throughout the publication and Figures and Scheme 1, teach methods for inducing antibacterial activity by introducing a multivalent ligand comprising a plurality of vancomycin residues, reading on signal recognition elements bonded to a ROMP-derived molecular scaffold of the formula of claim 82, that binds to D-Ala-D-Ala residue of the pentapeptide terminal of biosynthetic intermediates, which, absent evidence to the contrary, reads on a receptor of bacteria. Arimoto teaches at Scheme 1, polymers of the general formula of claims 82, 91 (where m=0 and n=2 or more) and 144.

The reference of Arimoto et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide.

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Arimoto et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

Response to Arguments

Applicant argues there is no teaching or suggestions that cellular chemotaxis can be induced by presenting a multivalent ligand having a signal recognition element that is N-formyl peptide.

Applicant's arguments, entered 1/17/2007, have been fully considered but they are not persuasive. Arimoto et al. teach ROMP multivalent ligands for increased

activity; and so provides motivation for combination with the methods of Schiffman for the use of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4).

20. Claims 17, 21-23, 28, 59, 60, 64, 68, 74, 90-92, 144, 148, 150, 157, 159, and 161-163 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kanai** et al., J. Am. Chem. Soc, 1997, Vol. 119 (41), pp. 1361-1362, (IDS filed 10/10/2002, ref. 45), in view of **Schiffman et al.**, US 4,427,660, (of record).

This rejection maintains the reasons of record as set forth in the previous Office action. This rejection is extended to claims newly added by amendment. The rejection is copied below for the convenience of the reader.

Kanai et al., throughout the publication, teach methods for inducing interference with erythrocyte agglutination mediated by the carbohydrate-binding protein concanavalin A by introducing multivalent ligands which posses a plurality of saccharide residues, which read on a plurality of signal recognition elements, that are covalently bonded (as in claim 74) to a ROMP-derived scaffold of the formula in claim 82. Kanai, at Table 1, teach more than 100 repeating units in the neoglycopolymer, as in claims 71-73. Kanai et al. teaches at Figure 1, polymers of the general formula of claims 82, 91 (where m=0 and n=2 or more) and 144. Concanavalin A induces an intracellular signal by increasing Ca^{2+} concentration in the cell, as evidenced by Ramaschi et al., (IDS filed 10/10/2002, ref. No. 76).

The reference of Kanai et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide.

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Kanai et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

Response to Arguments

Applicant argues is no teaching or suggestions that a chemoattractant bound to a multivalent ligand that is not an antibiotic would include chemotaxis in a similar manner to a chemoattractant bound to an antibiotic.

Applicant's arguments, entered 1/17/2007, have been fully considered but they are not persuasive. Kanai et al. teach ROMP multivalent ligands for increased efficacy in cell agglutination; and so provides motivation for combination with the methods of Schiffman for the use of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4).

Conclusion

21. Claims 17, 21-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 90-92, 140-148, 150, and 157-163 are rejected. No claims are allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Shibuya, whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark L. Shibuya, Ph.D.
Primary Examiner
Art Unit 1639

Notice to Comply	Application No.	Applicant(s)
	09/815,296	KIESSLING
	Examiner	Art Unit
	Shibuya	1639

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: Please see attached ~~sheets~~ action.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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